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Co-development of ADHD and externalizing behavior from childhood to adulthood

Abbreviated title: Co-development of ADHD and externalizing behavior

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Abstract

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) frequently co-occurs with externalizing disorders, but a clear understanding of the etiologic underpinnings is hampered by the limited understanding of the co-development of the traits from childhood into early adulthood.

Methods: Using a birth cohort of 2600 twins, the Swedish Twin study of Child and Adolescent Development study, assessed at ages 8-9, 13-14, 16-17 and 19-20, we investigated the co-development of ADHD and externalizing behavior from childhood to adulthood. The analyses examined ADHD-like and externalizing traits, as rated by twins and their parents using the Attention Problems scale and Externalizing scale of the Child Behavior Checklist, and estimated cross-lagged effects (one trait at one time-point predicting the other at the next). The covariation between the traits were decomposed into stable (effects carried over from the prior time-points) and innovative (new effects for each time-point) sources; each source was further decomposed into additive genetics, shared and non-shared environment.

Results: The analysis suggested that externalizing traits in middle childhood (age 8-9) predicted ADHD-like traits in early adolescence (age 13-14), whereas the reverse association was non-significant. In contrast, ADHD-like traits in mid-adolescence (age 16-17) predicted externalizing traits in early adulthood (age 19-20). The correlation between ADHD-like and externalizing traits increased over time. At all time-points innovative sources contributed substantially to maintained comorbidity. Genetic effects explained 67% of the covariation at each time-point; importantly, nearly 50% of these effects were innovative.

Conclusions: This study challenges the belief that ADHD generally precedes externalizing behaviors; rather, change in the etiologic factors across the development is the rule. The effects were due to both new genetic and environmental factors emerging up to young adulthood. Clinicians and researchers needs to consider complex etiologic and developmental models for the comorbidity between ADHD and externalizing behaviors.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a common neurodevelopmental disorder characterized by developmentally inappropriate and impairing levels of inattention, hyperactivity and impulsivity (Biederman & Faraone, 2005). ADHD frequently co-occurs with externalizing disorders; 30-50% of individuals meeting the criteria for ADHD also fulfill the criteria for Conduct Disorder (CD) or Oppositional Defiant Disorder (ODD) (Angold, Costello, & Erkanli, 1999; Biederman, Newcorn, & Sprich, 1991; Singh, 2008), and population-based studies suggest that ADHD-like and externalizing traits show considerable covariation in the general population (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003). Previous research has shown that ADHD is present in about 24-45% of adult prison inmates (Young & Thome, 2011), but little is known about the developmental trajectories leading to this serious outcome.

Although externalizing problems (e.g., ODD and CD symptoms) may occur early in life they are often assumed to be preceded by ADHD symptoms. Previous research has therefore mainly explored ADHD as a risk for later development of externalizing traits. Longitudinal studies of children with ADHD into adolescence and adult life suggest that externalizing outcomes such as antisocial personality disorder, criminality and substance abuse is more frequent among people with ADHD compared to children without psychopathology (Barkley, Fischer, Smallish, & Fletcher, 2004; Klein et al., 2012; Mannuzza, Klein, Abikoff, & Moulton, 2004; Satterfield et al., 2007). Some studies have shown that childhood ADHD predicts externalizing outcomes, even in the absence of co-occurring ODD and CD symptoms in childhood (Elkins, McGue, & Iacono, 2007), whereas other suggest that the elevated risk for externalizing outcomes disappears after controlling for co-morbid CD (Lahey, Loeber, Burke, Rathouz, & McBurnett, 2002; Lee,

Humphreys, Flory, Liu, & Glass, 2011; van Lier, van der Ende, Koot, & Verhulst, 2007). To our knowledge, only two studies has explored if externalizing traits influence later ADHD-like traits; a study of clinic-referred boys reporting that childhood CD predicted later ADHD symptoms, when early levels of ADHD were controlled, but not vice versa (Lahey et al., 2002), and a study where screening positive for conduct problems in boys aged 6 to 7 did not predict hyperactivity ratings at age 16 to 18 when controlling for a positive screening for conduct problems in childhood (Taylor, Chadwick, Heptinstall, & Danckaerts, 1996). Clearly, the dynamic relationship between ADHD-like and externalizing traits has not yet been adequately described, in particular during different developmental periods from childhood to adulthood.

Twin studies of ADHD-like traits among children and adolescents have consistently showed strong genetic influences, with heritability estimates around 60–90% (Burt, 2009; Faraone et al., 2005) whereas both genetic and shared environmental influences seem to be important for externalizing traits, especially during childhood (Burt, 2009; Rhee & Waldman, 2002). There is also evidence that the overlap between ADHD-like and externalizing traits, such as ODD and CD symptoms, are mainly of genetic origin (Dick, Viken, Kaprio, Pulkkinen, & Rose, 2005; Knopik et al., 2013; Nadder, Rutter, Silberg, Maes, & Eaves, 2002; Tuvblad, Zheng, Raine, & Baker, 2009); however, not all studies have reached that conclusion (Burt, Krueger, McGue, & Iacono, 2001).

Longitudinal twin studies have suggested that continuity in ADHD-like (Chang, Lichtenstein, Asherson, & Larsson, 2013) and externalizing traits (Wichers et al., 2013) is mainly due to genetic effects operating across time, and that developmental change in these traits is attributable to new genetic factors that emerge from childhood to early adulthood. Less is known about how stable and new factors contribute to comorbidity over time; in fact, no prior twin study has

explored how the comorbidity between ADHD-like and externalizing traits is maintained across the development from childhood to early adulthood. To investigate this we analyzed data collected at four waves from age 8 to age 20 in a Swedish population-based twin study, the Twin study of CHild and Adolescent Development (TCHAD; Lichtenstein, Tuvblad, Larsson, & Carlstrom, 2007). We aimed to; (1) explore the longitudinal direction of effects between ADHD-like and externalizing traits by simultaneously estimating the longitudinal phenotypic associations between the two traits when controlling for the preexisting associations. (2) Decompose the covariation between ADHD-like and externalizing traits at each time-point into components of stability (i.e., comorbidity maintained by stable sources) and innovation (i.e., comorbidity due to new sources). (3) Decompose these sources into their genetic and environmental etiologies.

Methods

Sample

TCHAD is a longitudinal cohort of all twins born in Sweden between May 1985 and December 1986. In total 1480 twin pairs have been invited, of which 2604 individuals (88.0%) from 1310 twin pairs (88.5%; 521 MZ [monozygotic] and 789 DZ [dizygotic] twin pairs) were included in the current study. Zygosity was determined using DNA testing or questions regarding physical similarity. Data was collected at ages 8-9 (middle childhood), 13-14 (early adolescence), 16-17 (late adolescence) and 19-20 (young adulthood). Response rates were 75%, 73%, 74% and 78% for parents (all time-points), and 78%, 82% and 59% for the twins (early adolescence to young adulthood) (Kendler, Gardner, & Lichtenstein, 2008; Lichtenstein et al., 2007). In young adulthood the twins were contacted to give consent before parents were approached with the

questionnaire. The study was approved by the regional ethics committee at Karolinska Institutet, Stockholm, Sweden. Informed consent was not required since Swedish rules states that response to the questionnaire constitutes consent.

Measures

Ratings of ADHD-like traits came from the Attention Problems scale (AP), ratings of externalizing traits came from the Externalizing scale (Ext), both scales are from the Achenbach System of Empirically Based Assessment (Achenbach, 1991a, 1991b; Achenbach & Rescorla, 2003). In middle childhood the Child Behavior Checklist (CBCL; Achenbach, 1991a) was used for parent-ratings; in early and late adolescence CBCL was used for parent-rating and Youth Self-Report (Achenbach, 1991b) was used for self-ratings; in young adulthood the Adult Behavior Checklist (Achenbach & Rescorla, 2003) was used for parent-ratings and Adult Self-Report (Achenbach & Rescorla, 2003) was used for self-ratings. Parents and twins were asked to rate the behavior within the past six months. Each construct (AP and Ext) consisted of several questions, each rated on a three-point scale (0 = not true; 1 = sometimes true; 2 = often true). The scales were the sum of the item scores; there was no item overlap across the two scales. Consistent with previous research, we used the AP-scale as a measure of ADHD (Chang et al., 2013), and the combination of two subscales of aggressive and delinquency/rule-breaking behaviors as the measure of Ext (Wichers et al., 2013). Both scales had a slightly skewed distribution and were therefore log-transformed before analysis.

Statistical analyses

The analysis is based on the assumptions in the twin method (Neale & Cardon, 1992); MZ twins share 100% of their co-segregating genes, while DZ twins on average share 50%. Furthermore,

MZ and DZ twin pairs are assumed affected by their shared environment to the same extent. The variance within, and covariance between, phenotypes is partitioned into additive genetic sources (*A*), shared (between twins in a pair) environmental sources (*C*), and environmental sources unique to each twin (*E*). To assess the appropriateness of performing analysis on the present data we performed a series of tests of equality of means and covariance matrices between twin order and zygosity (see **eAppendix A** for details). These analyses showed that models with more restrictions always was preferable to the less restricted (**eTable 1**), therefore we considered the data to be appropriate for analysis. The most restricted model (Model 5; **eTable 1**) was used for calculating correlations within and between twins in pairs.

To model the co-development of AP and Ext we used a cross-lagged model (Burt, McGue, Krueger, & Iacono, 2005) including the four time-points (**Figure 1**). In line with previous research (Chang et al., 2013; Kendler et al., 2008; Wichers et al., 2013), we used a measurement model that combines parent- and self-ratings to generate indexes of unobserved latent factors (AP_1-AP_4 and Ext_1-Ext_4) reflecting the shared view across raters. The measurement part of the model included rater-specific latent variables (F_{APP}, parent-rated AP; F_{APS}, self-rated AP; F_{ExtP} parent-rated Ext; F_{ExtS} self-rated Ext) to handle rater-bias. Each measurement had an error term (ε) to remove bias due to time-specific effects. Analyses of AP and Ext have earlier found to similar results between genders (Chang et al., 2013; Wichers et al., 2013); thus, we did not fit gender-specific models. However, each measure was adjusted for gender.

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Figure 1 about here

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The cross-lagged model constrains associations across age, after adjustment for rater and time-specific bias, to take the form of regression coefficients. The cross-age stability paths (β_{1121}, β_{1222}, β_{2131}, β_{2232}, β_{3141}, and β_{3242} in **Figure 1**) estimate the stability of AP and Ext, when controlling for the preexisting association between the two phenotypes. The cross-lagged paths estimate the independent contribution of AP at the earlier time-point on Ext at the consecutive time-point (β_{1122}, β_{2132} and β_{3142}) and the independent contribution of Ext at the earlier time-point on AP at the consecutive time-point (β_{1221}, β_{2231} and β_{3241}), while controlling for the stability in the two phenotypes. The variance and covariance of the latent constructs AP_1 and Ext_1 at time-point 8-9 was partitioned into *A*, *C* and *E* factors (Neale & Cardon, 1992). Similarly, at subsequent time-points, the residual (unexplained) variance and covariance of the latent constructs AP and Ext were decomposed into *A*, *C* and *E*. In **eAppendix B** the model is described in greater detail.

The cross-lagged model allowed us to simultaneously explore the direction and etiology of the longitudinal relationship between AP and Ext:

1. **Direction of effect:** The longitudinal direction of effects was inferred from the cross-age stability and cross-lagged paths.
2. **Stability and innovation:** Estimates for *A*, *C*, and *E* at each time-point, and cross-age stability and cross-lagged paths, were used to estimate covariation between AP and Ext and to identify the relative contribution of innovation and stability for maintained covariation.
3. **Genetic and environmental sources of covariance:** The estimates were also used to calculate the contributions from genetic and environmental sources in innovation and stability for maintained covariation.

eAppendix B describes how relevant parameters were calculated. For point 2 and 3 above we followed an approach suggested in Greven, Rijsdijk, Asherson, and Plomin (2012) to analyze the covariance rather than each variance separately, because we focused on the co-development of AP and Ext. All analyses were performed using the package OpenMx (S. Boker et al., 2011; S. M. Boker et al., 2012) in the software R (R Development Core Team, 2013), where full information maximum likelihood was employed to handle missing data. Confidence intervals were calculated as 95% profile likelihood confidence intervals.

Results

Descriptive

Twin correlations (i.e., within-twin pair maximum likelihood correlations) are reported in **Table 1**. MZ-twin correlations were generally twice that of DZ-twins, for example, for parent-rating of Ext at age 8-9 MZ twins had a correlation of 0.67 while DZ twins had a correlation of 0.37. For each phenotype at each time-point, the correlations between raters were moderate; ranging from 0.34 to 0.42 (**eTable 2**). The correlations between the phenotypes, within rater, at each time-point were higher; between 0.54 and 0.61 (**eTable 2**). The phenotypic stability (within rater) was highest between two adjacent time-points, and declined as the time-points were further apart (**eTable 2**). Correlations between twins in pairs for different raters and/or time-points and/or traits were higher in MZ compared to DZ twins in all but two instances, indicating that genetic effects are important also for the comorbidity and over development (**eTable 3**).

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Table 1 about here

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The cross-lagged model

We fitted the cross-lagged model; the most important results are presented in **Figure 2** and **3**, the standardized genetic and environmental variance components are found in **eTable 4**, whereas all parameters estimates from the model are presented in **eTable 5**.

Direction of effects

All standardized stability paths were large (0.52-0.88) and significant, that is, each phenotype at one time-point was predicted by the same phenotype at the previous time-point, while adjusting for the other phenotype at the previous time-point (**Figure 2**). Only two out of the potential six cross-lagged paths were significantly different from zero; Ext at age 8-9 predicted AP at age 13-14, with a standardized regression coefficient of 0.18, and AP at age 16-17 predicted Ext at age 19-20, with a standardized regression coefficient of 0.13 (**Figure 2**). To quantify the effect sizes of the cross-lagged paths we may compare them to the effect sizes of the corresponding stability paths; one standard deviation (SD) increase in AP at age 8-9 predicted a 0.52 SD increase in AP at age 13-14 while one SD increase in Ext at age 8-9 predicted a 0.18 SD increase in AP at age 13-14. At age 16-17 one SD increase in AP and Ext predicted 0.13 and 0.67 SD increase in Ext at age 19-20, respectively.

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Figure 2 about here

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Stability and innovation

Figure 3 shows the phenotypic correlation between AP and Ext, as well as the relative contribution of innovation and stability to the observed correlations. The phenotypic correlations (i.e., the correlations between the latent AP and Ext constructs are shown on Y-axis of **Figure 3**) were 0.63, 0.70, 0.82, and 0.84 at the consecutive time-points. To test whether the correlations were significantly different across time-points we fitted a model where they were constrained to be equal. The model fitted poorer regardless if all four time-points were assumed equal (likelihood ratio test (LRT): $\chi^2 = 36.30$, df = 3, p-value < 0.001) or just the last three (LRT: $\chi^2 = 20.78$, df = 2, p-value < 0.001), suggesting that the covariation between AP and Ext increase over time. We did not observe any increasing or decreasing pattern of covariance explained by innovation and stability; 49%, 63% and 54% of the covariance was accounted for by innovation sources at the last three time-points (**Figure 3**).

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Figure 3 about here

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Genetic and environmental sources of covariance

Figure 3 also shows the genetic and environmental contribution to the correlation between AP and Ext. At the last three time-points *A, C* and *E* was partitioned into stable and innovation effects. The fraction of the covariation explained by genetic effects (stability and innovation) could be assumed to be the same across the different time-points; that is, a model where the fractions of genetic effects were assumed equal at 67% across time-points did not yield a poorer fit (LRT: $\chi^2 = 5.50$, df = 3, p-value = 0.138). Forty-six per cent of the genetic effects were from

innovation sources (i.e., the remaining 54% of the genetic covariance was due to genetic stability); a model constraining the relative contribution of innovation *A* to be constant at 46% over the last three time-points did not fit the data worse (LRT: $\chi^2 = 2.02$, df = 2, p-value = 0.364).

Discussion

Contrary to the established view that ADHD is preceding externalizing behaviors, we found that externalizing traits in middle childhood influenced ADHD-like traits in early adolescence. However, ADHD-like traits in late adolescence influenced externalizing traits in early adulthood, which is consistent with the notion that childhood ADHD contributes independently to antisocial personality disorder, criminality and substance abuse in adulthood (Barkley et al., 2004; Elkins et al., 2007; Lee et al., 2011; Satterfield et al., 2007). The correlation between the traits increased across age, thus the correlation between ADHD-like and externalizing traits in adulthood is not only due to pre-existing associations between the traits (Lynam, 1996). Interestingly, genetic innovation explained a significant part of this overlap, indicating that change in the etiologic factors is the rule, rather than the exception. The combination of these findings indicates that both clinicians and researchers need to consider complex etiologic and developmental models for the comorbidity of ADHD and externalizing behaviors. For instance, our finding that childhood externalizing traits predicts elevated levels of ADHD symptoms in adolescence may challenge the validity of the DSM age-at-onset criterion for ADHD.

Our study extends previous findings by suggesting that the pattern of co-development change across time. One study specifically exploring the potential importance of a dynamic co-development of ADHD-like and externalizing traits suggest that childhood externalizing

problems predicts subsequent levels of ADHD (Lahey et al., 2002); we replicate this finding. Our finding of no direct longitudinal association between ADHD-like traits in mid-childhood and externalizing traits in early adolescence, adjusting for pre-existing overlaps between the traits, is also in line with some of the previous research (Lahey et al., 2002; Lee et al., 2011; van Lier et al., 2007). We observed non-significant cross-lagged effects from early adolescence to late adolescence. This finding is novel and may suggest that the co-occurrence of ADHD-like and externalizing traits is stable during this developmental period. In contrast to the developmental relationship observed from childhood to early adolescence (i.e., externalizing traits predict ADHD-like traits), the reverse association was observed from mid-adolescence to early adulthood, indicating that ADHD-like traits may exacerbate externalizing tendencies in the transition from adolescence into adult life.

As expected, we found high correlations between ADHD-like and externalizing traits at all time-point from childhood to adulthood (Angold et al., 1999; Biederman et al., 1991; Costello et al., 2003; Singh, 2008; Young & Thome, 2011). Our data indicate that the correlations between ADHD-like and externalizing traits in adolescence and adulthood was partly due to stable sources of covariation, which is consistent with the view that the comorbidity originates early and remains stable over time. This is in line with research showing that children with ADHD plus externalizing problems are at increased risk for a similar behavioral profile in adulthood (Lynam, 1996). Here we demonstrate that the magnitude of the covariation increase over time and that innovative effects were equally important as stable sources. Clearly, future attempts to understand the development of the comorbidity between ADHD and externalizing traits needs to use longitudinal data and consider both stable and time-varying factors.

In line with previous research, we found that the overlap between ADHD-like and externalizing traits was largely explained by shared genetic factors (Dick et al., 2005; Knopik et al., 2013; Nadder et al., 2002; Tuvblad et al., 2009). Particularly, one study has shown that the covariation between the two traits across time is governed by genetics (Nadder et al., 2002). Our results confirms these findings and moreover suggests that stable shared environment factors may contribute to the covariation between ADHD-like and externalizing traits in early adolescence. This finding needs to be interpreted carefully as most (Dick et al., 2005; Knopik et al., 2013; Nadder et al., 2002; Tuvblad et al., 2009), but not all (Burt et al., 2001), studies suggest that shared environmental sources of variation has a limited impact on ADHD-like traits. More importantly, the present study extends previous research by showing that the increased correlation between ADHD-like and externalizing traits from childhood to early adulthood was largely due to new genetic factors. This is in line with previous results where support for the "developmentally dynamic" hypothesis (i.e., genetic innovation explain significant fractions of the variation throughout development) was found when ADHD-like (Chang et al. 2013) and externalizing (Wichers et al. 2013) traits were studied separately. There are examples of widespread pleiotropic effects of genetic risk variants for psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Our finding of genetic innovation does not rule out pleiotropic effects for ADHD-like and externalizing traits, but suggests that at least part of these influences are developmental specific.

Strength and limitations

One of the strengths of this study is that is uses a representative sample; all twins born during approximately 18 months in Sweden were invited to participate. The data used have been collected prospectively in four waves from mid-childhood to young adulthood. We have utilized

as much information as possible by including multiple informants; this allowed us to try and isolate a shared view of the traits measured, and remove rater-bias. Researchers have previously argued that this approach produces more valid inferences since it includes subjective and objective views of the constructs and accounts for rater-specific changes over development (Chang et al., 2013; Kendler et al., 2008; Wichers et al., 2013).

A limitation of this study is that the associations across time-points are forced to go through the cross-age stability and cross-lagged paths. This puts a constraint on how genetic and environmental factors influences subsequent time-points, i.e. the stability contributions to covariance. This is in contrast to the "Cholesky decomposition" approach, used in for example previous studies of the two traits in this sample (Chang et al., 2013; Wichers et al., 2013), where genetic and environmental factors are allowed to more freely influence the measures at later time-points.

The fact that we are using a population-based sample and quantitative measures of ADHD and externalizing problems, rather than clinically diagnosed ADHD, may limit the generalizability to more extreme forms of ADHD. However, we have recently observed a strong genetic link between the extreme and the sub-threshold variation of ADHD symptoms, suggesting that the same etiologic factors are involved in the full range of symptoms of inattention, hyperactivity and impulsivity (Larsson, Chang, D'Onofrio, & Lichtenstein, 2013).

Although the sample has relatively high response-rates in the younger ages, the attrition is not insignificant, with the lowest response-rate for the twins in young adulthood of 59%. If the responders are not representative of the cohort, the parameter estimates (especially in the older ages) might be biased.

Conclusions

This study challenges a simplistic view of ADHD as a stable condition that co-occurs with externalizing behavior because of early emerging stable factors. Our findings provide an empirical foundation for more developmentally-dynamic theories of the comorbidity. Future research that aims to enhance our understanding of the mechanisms underlying the co-development of ADHD and externalizing disorders needs to take bi-directional relationships and time-varying etiologic factors (i.e., genetic and environmental innovation) into consideration.

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Key points

- ADHD and externalizing/anti-social behaviors frequently co-occur; the etiology of this comorbidity is not well investigated.
- Using a longitudinal assessed twin cohort we disentangled stable and emerging sources of covariation between the traits.
- Externalizing traits predicted ADHD-like traits from middle childhood to early adolescence while ADHD-like traits predicted externalizing traits from late adolescence to young adulthood.
- About 50% of the covariation between the traits was attributable to previous measures of the traits, and 50% to newly emerging sources; a majority of which were genetic.
- The development of comorbidity of ADHD and externalizing behavior seems to be more dynamic than generally considered, future research and clinical practitioners need to take bi-directionality and emerging factors into consideration.

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Figures

Figure 1: The model. Note that the figure display the model within an individual, the full model also includes associations between twin pairs.

Footnote: Time-points are numbere 1 to 4 representing ages 8-9, 13-14, 16-17 and 19-20. ACE indicates that the latent variables are decomposed into additive genetic-, shared environmental-, and non-shared environmental- parts. AP, attention problems; Ext, externalizing/disruptive behavior; P, parent-rating; S, self-rating; ACE at time-point 2-4 represent residual variance and covariance, and ε represent residual variance. The path diagram is not a complete representation of the model, more complete path diagrams are found in **eFigure 1a** and **b**.

Figure 2: Standardized cross-age stability paths and cross-lagged paths.

Footnote: Bold figures and solid lines represent estimates where the confidence interval does not overlap the zero. Time-points are numbere 1 to 4 representing ages 8-9, 13-14, 16-17 and 19-20. AP, attention problems. Ext, externalizing behavior.

Figure 3: Genetic and environmental effects in the co-development of attention problems and externalizing behavior as expressed by the correlation between constructs at each time-point.

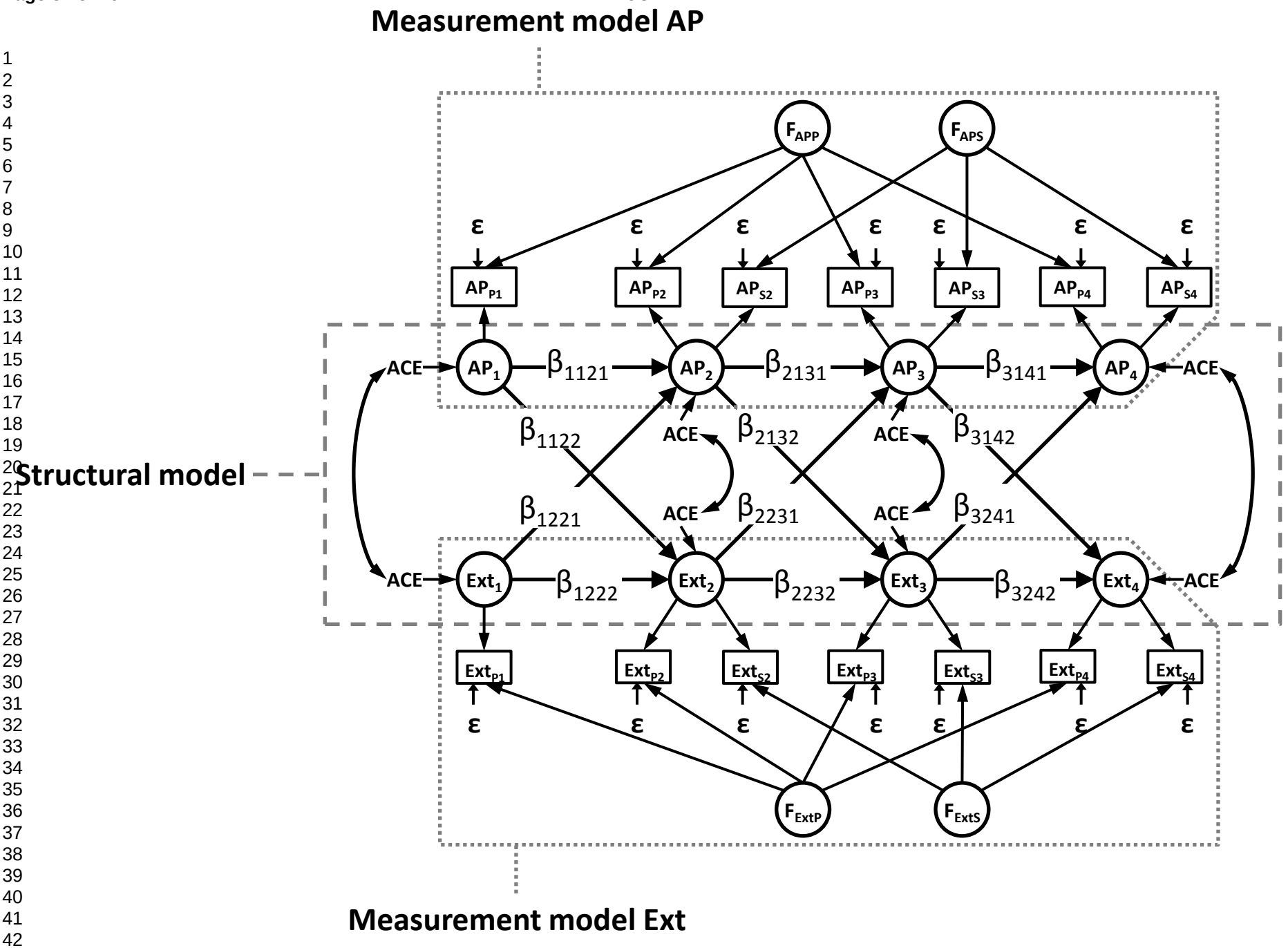
Footnote: "Stable" refers to correlation explained by earlier time-points, "Innovation" refers to correlation explained by effect that are new at the time-point. *A*, additive genetic effects. *C*, shared environmental effects. *E*, non-shared environmental effects.

Tables

Table 1: Intra-class (within twin pair) correlations.

Attention problems		MZ	DZ
Age 8-9	Parent report	0.44	0.19
Age 13-14	Parent report	0.44	0.25
	Self report	0.38	0.22
Age 16-17	Parent report	0.49	0.21
	Self report	0.34	0.16
Age 19-20	Parent report	0.52	0.19
	Self report	0.30	0.18
Externalizing behavior			
Age 8-9	Parent report	0.67	0.37
Age 13-14	Parent report	0.73	0.48
	Self report	0.34	0.18
Age 16-17	Parent report	0.79	0.53
	Self report	0.32	0.17
Age 19-20	Parent report	0.54	0.28
	Self report	0.35	0.14

Footnote: Values as estimated in Model 5, **eTable 1**.


Measurement model AP
Structural model
Measurement model Ext
F_APP
F_APS
ε
AP_P1
AP_P2
AP_S2
AP_P3
AP_S3
AP_P4
AP_S4
ACE
AP_1
AP_2
AP_3
AP_4
β_1121
β_2131
β_3141
β_1122
β_2132
β_3142
β_1221
β_2231
β_3241
Ext_1
Ext_2
Ext_3
Ext_4
β_1222
β_2232
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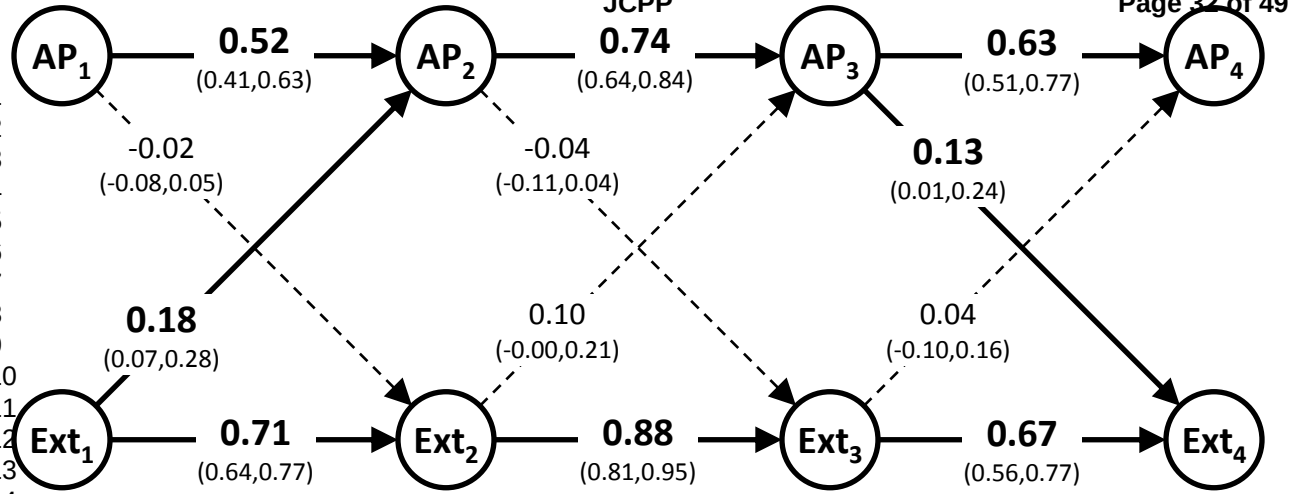
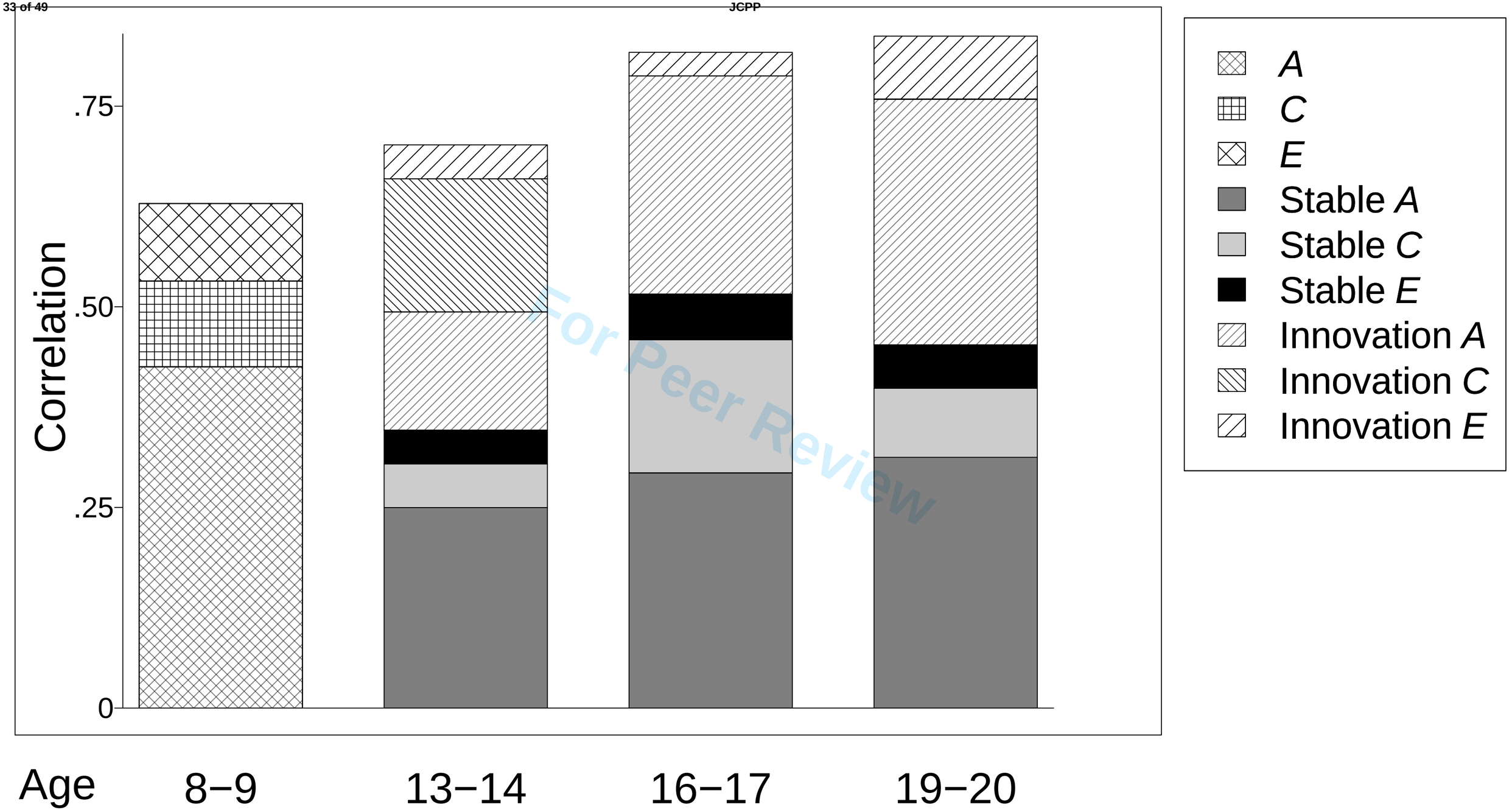
Ext_S3
Ext_P4
Ext_S4
F_ExtP
F_ExtS


AP1
AP2
AP3
AP4
Ext1
Ext2
Ext3
Ext4
0.52
(0.41,0.63)
0.74
(0.64,0.84)
0.63
(0.51,0.77)
-0.02
(-0.08,0.05)
-0.04
(-0.11,0.04)
0.13
(0.01,0.24)
0.18
(0.07,0.28)
0.10
(-0.00,0.21)
0.04
(-0.10,0.16)
0.71
(0.64,0.77)
0.88
(0.81,0.95)
0.67
(0.56,0.77)



The mechanisms behind the co-development of ADHD and externalizing behavior from childhood to adulthood

Online supplemental material

Ralf Kuja-Halkola, Paul Lichtenstein, Brian M D'Onofrio, Henrik Larsson

Contents

eAppendix A: Test of appropriateness of analysis

We used the Bayesian Information Criterion (BIC) and likelihood ratio tests to evaluate the fit of models. These tests were performed to be certain that twins are (1) comparable in gender-adjusted means between twin order and zygosity, (2) comparable in covariance between measurements within individual regardless of twin order and zygosity, and (3) symmetric in covariances between twin order (i.e. that the covariance of measure X in twin 1 with measure Y in twin 2 is similar to the covariation of measure X in twin 2 with measure Y in twin 1). If these criteria are fulfilled we can treat the data as exchangeable within individuals regardless of twin order and zygosity, and across twins regardless of twin order (separately per zygosity). We base our model on these assumptions.

Test of assumptions

We began by fitting a free model where all covariances were estimated independently, and means estimated separately and adjusted for gender (Model 1). We tested whether adjustment for gender on the mean values could be assumed to be equal between zygosity and twin order (Model 2). We then equated the means between zygosity type and twin order (Model 3) to see whether this lead to a worse model fit. A model where the covariances within individuals were assumed to be the same regardless of twin order as well as zygosity (Model 4) was then compared to the previous models. Finally we tested whether the between twin covariances could be assumed symmetric within each zygosity separately (Model 5). Model fitting is presented in **eTable 1**; the BIC indicated that the more restricted models was always preferable to the less restricted, furthermore a likelihood ratio test indicated that Model 5 did not have a significantly worse fit than the least restricted Model 1 (difference in -2 log likelihood = 625.10, difference in degrees of freedom = 581, p-value = 0.100), suggesting that the assumptions were not violated.

eTable 1: Testing of assumptions for quantitative genetic modeling.

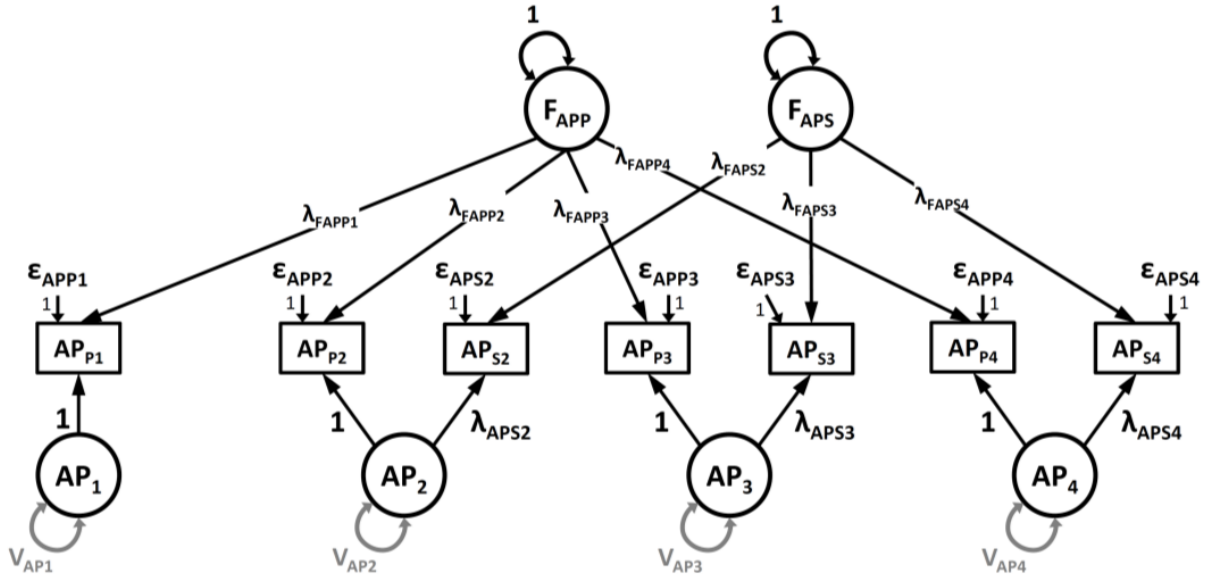
Model	Estimated Parameters (EP)	- 2 Log Likelihood (-2LL)	Difference in EP compared to Model 1	Difference in -2LL compared to Model 1	Bayesian information criterion
1: Unrestricted model	924	42421.40	0	0	49053.67
2: Mean differences by gender assumed to be equal across twin order and zygosity	882	42462.26	42	40.86	48793.07
3: As model 2 and means equal between twin order and zygosity	840	42550.18	84	128.78	48579.52
4: As model 3 and covariances within individuals equal across twin order and zygosity	525	42846.89	399	425.49	46615.23
5: As model 4 and symmetric covariances between twins in zygosity groups	343	43046.50	581	625.10	45508.48

Footnote: Lower values for Bayesian information criterion indicates preferred model.

eAppendix B: Model description

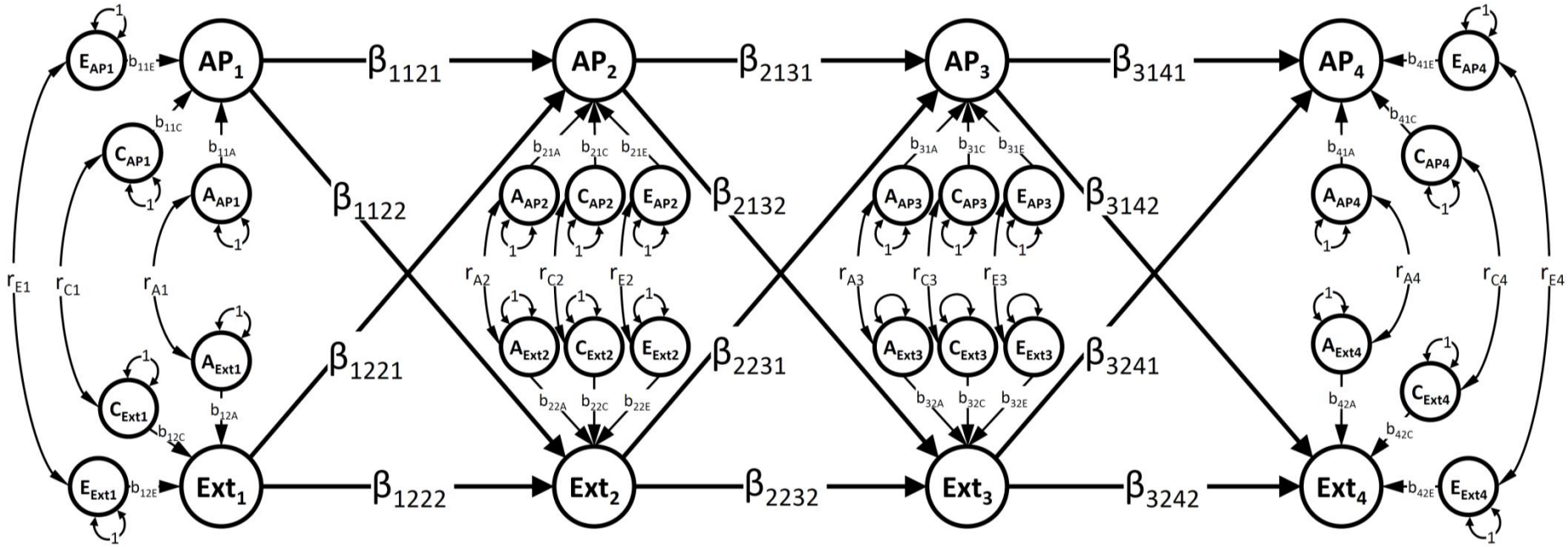
Here the model is explained in greater detail than in the main paper. Within an individual we may focus on two parts of the model; (1) The measurement model for AP and Ext, and (2) the structural model, including the quantitative genetic estimates. In **Figure 1** in the main paper a sketch of the full model within a subject is seen. In **eFigure 1a** and **1b** the measurement model and structural model are shown in greater detail. In these figures all estimated parameters are implied except means and regression on gender for the measured variables (14+14=28 parameters). Also not shown are the correlation between parent-rater effect (F_{APP} and F_{ExtP}) and self-rater effect (F_{APS} and F_{ExtS}) between twins in a pair, which is allowed to differ between zygosity (4+4=8 parameters).

eFigure 1a: Measurement model for AP, the measurement model for Ext is similarly defined.



Footnote: Circles indicates latent variables, boxes measured variables. The variance of AP_1 – AP_4 are separated into additive genetic (*A*), shared environment (*C*) and non-shared environment (*E*).

eFigure 1b: The structural model, including cross-age stability paths, cross-lagged paths and quantitative genetic partitioning of variance.



Footnote: Circles indicates latent variables. The variance of AP_1 – AP_4 and Ext_1 – Ext_4 are separated into additive genetic (*A*), shared environment (*C*) and non-shared environment (*E*).

Model setup

Below follows a mathematical description of the model.

The structural part of the structural equation model is set up in the following way:

$$\boldsymbol{\eta}_{ij} = \boldsymbol{B}\boldsymbol{\eta}_{ij} + \boldsymbol{\Gamma}\boldsymbol{\xi}_{ij} + \boldsymbol{\zeta}_{ij}, \tag{1}$$

where i (=1,2,…,N; N = number of twin pairs) is the twin pair number and j (=1,2) is the twin number, and $\boldsymbol{\eta}_{ij}$, $\boldsymbol{\xi}_{ij}$ and $\boldsymbol{\zeta}_{ij}$ are latent, unobserved, variables, and $\boldsymbol{B}$ and $\boldsymbol{\Gamma}$ are matrices of regression parameters;

$$\begin{aligned}
&\boldsymbol{\xi}_{ij} = \left(AP_{1ij}, Ext_{1ij}\right)^T, \\
&\boldsymbol{\eta}_{ij} = \left(AP_{2ij}, Ext_{2ij}, AP_{3ij}, Ext_{3ij}, AP_{4ij}, Ext_{4ij}\right)^T, \\
&\boldsymbol{\zeta}_{ij} = \left(\zeta_{AP2ij}, \zeta_{Ext2ij}, \zeta_{AP3ij}, \zeta_{Ext3ij}, \zeta_{AP4ij}, \zeta_{Ext4ij}\right)^T, \\
&\boldsymbol{B} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 \\ \beta_{2131} & \beta_{2231} & 0 & 0 & 0 & 0 \\ \beta_{2132} & \beta_{2232} & 0 & 0 & 0 & 0 \\ 0 & 0 & \beta_{3141} & \beta_{3241} & 0 & 0 \\ 0 & 0 & \beta_{3142} & \beta_{3242} & 0 & 0 \end{bmatrix}, \\
&\boldsymbol{\Gamma} = \begin{bmatrix} \beta_{1121} & \beta_{1221} \\ \beta_{1122} & \beta_{1222} \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}.
\end{aligned} \tag{2}$$

Furthermore there are some covariance matrices involved regarding the variables $\boldsymbol{\xi}_{ij}$ and $\boldsymbol{\zeta}_{ij}$:

$$Cov\left(\boldsymbol{\xi}_{ij}\right) = \boldsymbol{\Phi} = \begin{bmatrix} b_{11A}^2 + b_{11C}^2 + b_{11E}^2 & r_{A1}b_{11A}b_{12A} + r_{C1}b_{11C}b_{12C} + r_{E1}b_{11E}b_{12E} \\ r_{A1}b_{11A}b_{12A} + r_{C1}b_{11C}b_{12C} + r_{E1}b_{11E}b_{12E} & b_{12A}^2 + b_{12C}^2 + b_{12E}^2 \end{bmatrix},$$

$$Cov\left(\boldsymbol{\zeta}_{ij}\right) = \boldsymbol{\Psi}$$

$$= \begin{bmatrix} b_{21A}^2 + b_{21C}^2 + b_{21E}^2 & r_{A2}b_{21A}b_{22A} + r_{C2}b_{21C}b_{22C} + r_{E2}b_{21E}b_{22E} & \cdots \\ r_{A2}b_{21A}b_{22A} + r_{C2}b_{21C}b_{22C} + r_{E2}b_{21E}b_{22E} & b_{22A}^2 + b_{22C}^2 + b_{22E}^2 & \\ 0 & 0 & \cdots \\ 0 & 0 & \\ 0 & 0 & \cdots \\ 0 & 0 & \end{bmatrix}$$

$$\begin{bmatrix} \cdots & 0 & 0 & \cdots \\ & 0 & 0 & \\ \cdots & b_{31A}^2 + b_{31C}^2 + b_{31E}^2 & r_{A3}b_{31A}b_{32A} + r_{C3}b_{31C}b_{32C} + r_{E3}b_{31E}b_{32E} & \cdots \\ \cdots & r_3b_{31A}b_{32A} + r_{C3}b_{31C}b_{32C} + r_{E3}b_{31E}b_{32E} & b_{32A}^2 + b_{32C}^2 + b_{32E}^2 & \\ \cdots & 0 & 0 & \cdots \\ & 0 & 0 & \end{bmatrix}$$

$$\begin{bmatrix} 0 & 0 \\ \cdots & 0 & 0 \\ & 0 & 0 \\ \cdots & 0 & 0 \\ & b_{41A}^2 + b_{41C}^2 + b_{41E}^2 & r_{A4}b_{41A}b_{42A} + r_{C4}b_{41C}b_{42C} + r_{E4}b_{41E}b_{42E} \\ \cdots & r_{A4}b_{41A}b_{42A} + r_{C4}b_{41C}b_{42C} + r_{E4}b_{41E}b_{42E} & b_{42A}^2 + b_{42C}^2 + b_{42E}^2 \end{bmatrix}. \tag{3}$$

Note that $\mathbf{\Psi}$ captures the innovation effects at time-points 2, 3 and 4. The "b"-parameters are estimated by including MZ and DZ twin pairs in the analysis; Let g_i be the genetic similarity of twin pair i, which is 1 for MZ twins and 0.5 for DZ twins. The covariance between twins is thus

$$Cov(\boldsymbol{\xi}_{i1}, \boldsymbol{\xi}_{i2}) = \mathbf{\Phi}_{\mathrm{MZ/DZ}} = \begin{bmatrix} g_i \cdot b_{11A}^2 + b_{11C}^2 & g_i \cdot r_{A1} b_{11A} b_{12A} + r_{C1} b_{11C} b_{12C} \\ g_i \cdot r_{A1} b_{11A} b_{12A} + r_{C1} b_{11C} b_{12C} & g_i \cdot b_{12A}^2 + b_{12C}^2 \end{bmatrix},$$

$$Cov(\boldsymbol{\zeta}_{i1}, \boldsymbol{\zeta}_{i2}) = \mathbf{\Psi}_{\mathrm{MZ/DZ}} =$$

$$\begin{bmatrix} g_i \cdot b_{21A}^2 + b_{21C}^2 & g_i \cdot r_{A2} b_{21A} b_{22A} + r_{C2} b_{21C} b_{22C} & 0 & 0 & 0 & 0 \\ g_i \cdot r_{A2} b_{21A} b_{22A} + r_{C2} b_{21C} b_{22C} & g_i \cdot b_{22A}^2 + b_{22C}^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & g_i \cdot b_{31A}^2 + b_{31C}^2 & g_i \cdot r_{A3} b_{31A} b_{32A} + r_{C3} b_{31C} b_{32C} & 0 & 0 \\ 0 & 0 & g_i \cdot r_{A3} b_{31A} b_{32A} + r_{C3} b_{31C} b_{32C} & g_i \cdot b_{32A}^2 + b_{32C}^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & g_i \cdot b_{41A}^2 + b_{41C}^2 & g_i \cdot r_{A4} b_{41A} b_{42A} + r_{C4} b_{41C} b_{42C} \\ 0 & 0 & 0 & 0 & g_i \cdot r_{A4} b_{41A} b_{42A} + r_{C4} b_{41C} b_{42C} & g_i \cdot b_{42A}^2 + b_{42C}^2 \end{bmatrix}. \quad (4)$$

The measurement part of the model is set up as follows:

$$\begin{bmatrix} \boldsymbol{x}_{ij} \\ \boldsymbol{y}_{ij} \end{bmatrix} = \boldsymbol{m} + \boldsymbol{\alpha} \cdot sex_{ij} + \begin{bmatrix} \mathbf{\Lambda}_x \boldsymbol{\xi}_{ij} + \boldsymbol{\varepsilon}_{xij} \\ \mathbf{\Lambda}_y \boldsymbol{\eta}_{ij} + \boldsymbol{\varepsilon}_{yij} \end{bmatrix} + \mathbf{\Lambda}_F \boldsymbol{\xi}_{Fij}, \quad (5)$$

where sex_{ij} is the gender of twin j in twin pair i (=0 if male and =1 if female), and

$$\boldsymbol{x}_{ij} = \left(AP_{P1ij}, Ext_{P1ij}\right)^T,$$
$$\boldsymbol{y}_{ij} = \left(AP_{P2ij}, AP_{S2ij}, Ext_{P2ij}, Ext_{S2ij}, AP_{P3ij}, AP_{S3ij}, Ext_{P3ij}, Ext_{S3ij}, AP_{P4ij}, AP_{S4ij}, Ext_{P4ij}, Ext_{S4ij}\right)^T,$$
$$\boldsymbol{m} = (m_{APP1}, m_{ExtP1}, m_{APP2}, m_{APS2}, m_{ExtP2}, m_{ExtS2}, m_{APP3}, m_{APS3}, m_{ExtP3}, m_{ExtS3}, m_{APP4}, m_{APS4}, m_{ExtP4}, m_{ExtS4})^T,$$
$$\boldsymbol{\alpha} = (\alpha_{APP1}, \alpha_{ExtP1}, \alpha_{APP2}, \alpha_{APS2}, \alpha_{ExtP2}, \alpha_{ExtS2}, \alpha_{APP3}, \alpha_{APS3}, \alpha_{ExtP3}, \alpha_{ExtS3}, \alpha_{APP4}, \alpha_{APS4}, \alpha_{ExtP4}, \alpha_{ExtS4})^T,$$
$$\mathbf{\Lambda}_x = \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix},$$
$$\mathbf{\Lambda}_y = \begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ \lambda_{APS2} & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & \lambda_{ExtS2} & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & \lambda_{APS3} & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & 0 \\ 0 & 0 & 0 & \lambda_{ExtS3} & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 0 & \lambda_{APS4} & 0 \\ 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 0 & \lambda_{Ext4} \end{bmatrix}, \quad (6)$$

$$\boldsymbol{\varepsilon}_{xij} = \left(\varepsilon_{APP1ij}, \varepsilon_{ExtP1ij}\right)^T,$$
$$\boldsymbol{\varepsilon}_{yij} = \left(\varepsilon_{APP2ij}, \varepsilon_{APS2ij}, \varepsilon_{ExtP2ij}, \varepsilon_{ExtS2ij}, \varepsilon_{APP3ij}, \varepsilon_{APS3ij}, \varepsilon_{ExtP3ij}, \varepsilon_{ExtS3ij}, \varepsilon_{APP4ij}, \varepsilon_{APS4ij}, \varepsilon_{ExtP4ij}, \varepsilon_{ExtS4ij}\right)^T,$$
$$\boldsymbol{\Lambda}_F = \begin{bmatrix} \lambda_{FAPP1} & 0 & 0 & 0 \\ 0 & 0 & \lambda_{FExtP1} & 0 \\ \lambda_{FAPP2} & 0 & 0 & 0 \\ 0 & \lambda_{FAPS2} & 0 & 0 \\ 0 & 0 & \lambda_{FExtP2} & 0 \\ 0 & 0 & 0 & \lambda_{FExtS2} \\ \lambda_{FAPP3} & 0 & 0 & 0 \\ 0 & \lambda_{FAPS3} & 0 & 0 \\ 0 & 0 & \lambda_{FExtP3} & 0 \\ 0 & 0 & 0 & \lambda_{FExtS3} \\ \lambda_{FAPP4} & 0 & 0 & 0 \\ 0 & \lambda_{FAPS4} & 0 & 0 \\ 0 & 0 & \lambda_{FExtP4} & 0 \\ 0 & 0 & 0 & \lambda_{FExtS4} \end{bmatrix},$$
$$\boldsymbol{\xi}_{Fij} = \left(F_{APPij}, F_{APSij}, F_{ExtPij}, F_{ExtSij}\right)^T.$$

Also here variances/covariances for latent variables are included;

$$\begin{aligned} &Cov\left(\boldsymbol{\varepsilon}_{xij}\right) = \boldsymbol{\Theta}_x = diag(\sigma^2_{APP1}, \sigma^2_{ExtP1}), \\ &Cov\left(\boldsymbol{\varepsilon}_{yij}\right) = \boldsymbol{\Theta}_y \\ &= diag(\sigma^2_{APP2}, \sigma^2_{APS2}, \sigma^2_{ExtP2}, \sigma^2_{ExtS2}, \sigma^2_{APP3}, \sigma^2_{APS3}, \sigma^2_{ExtP3}, \sigma^2_{ExtS3}, \sigma^2_{APP4}, \sigma^2_{APS4}, \sigma^2_{ExtP4}, \sigma^2_{ExtS4}), \\ &Cov\left(\boldsymbol{\xi}_{Fij}\right) = diag(1,1,1,1), \\ &Cov(\boldsymbol{\xi}_{Fi1}, \boldsymbol{\xi}_{Fi2}) = \boldsymbol{\Phi}_{FMZ} = diag(r_{FAPPMZ}, r_{FAPSMZ}, r_{FExtPMZ}, r_{FExtSMZ}), \text{ for MZ twin pairs, and} \\ &Cov(\boldsymbol{\xi}_{Fi1}, \boldsymbol{\xi}_{Fi2}) = \boldsymbol{\Phi}_{FDZ} = diag(r_{FAPPDZ}, r_{FAPSDZ}, r_{FExtPDZ}, r_{FExtSDZ}), \text{ for DZ twin pairs,} \end{aligned} \quad (7)$$

where $diag$ refers to a diagonal matrix. All possible covariances not mentioned in equations (1)-(7) are assumed to be zero. The model is represented by a total of 118 parameters.

The modeled covariance matrix, within a twin in a pair, assuming the fixed effects in $\boldsymbol{m}$ and $\boldsymbol{\alpha}$ known and adjusted for, can be written as

$$Cov\left(\begin{bmatrix}\boldsymbol{x}_{ij} \\ \boldsymbol{y}_{ij}\end{bmatrix}\right) = Cov\left(\begin{bmatrix}\boldsymbol{\Lambda}_x\boldsymbol{\xi}_{ij} + \boldsymbol{\varepsilon}_{xij} \\ \boldsymbol{\Lambda}_y\boldsymbol{\eta}_{ij} + \boldsymbol{\varepsilon}_{yij}\end{bmatrix} + \boldsymbol{\Lambda}_F\boldsymbol{\xi}_{Fij}\right) = Cov\left(\begin{bmatrix}\boldsymbol{\Lambda}_x\boldsymbol{\xi}_{ij} + \boldsymbol{\varepsilon}_{xij} \\ \boldsymbol{\Lambda}_y\boldsymbol{\eta}_{ij} + \boldsymbol{\varepsilon}_{yij}\end{bmatrix}\right) + Cov\left(\boldsymbol{\Lambda}_F\boldsymbol{\xi}_{Fij}\right). \quad (8)$$

To find the solution note that latent variable $\boldsymbol{\eta}_{ij}$ may be expressed in terms of latent variables $\boldsymbol{\xi}_{ij}$ and $\boldsymbol{\zeta}_{ij}$. From equation (1) we have

$$\begin{aligned} &\boldsymbol{\eta}_{ij} = \boldsymbol{B}\boldsymbol{\eta}_{ij} + \boldsymbol{\Gamma}\boldsymbol{\xi}_{ij} + \boldsymbol{\zeta}_{ij} \Leftrightarrow \\ &\boldsymbol{\eta}_{ij} - \boldsymbol{B}\boldsymbol{\eta}_{ij} = \boldsymbol{\Gamma}\boldsymbol{\xi}_{ij} + \boldsymbol{\zeta}_{ij} \Leftrightarrow \\ &(\boldsymbol{I} - \boldsymbol{B})\boldsymbol{\eta}_{ij} = \boldsymbol{\Gamma}\boldsymbol{\xi}_{ij} + \boldsymbol{\zeta}_{ij} \Leftrightarrow \\ &\boldsymbol{\eta}_{ij} = (\boldsymbol{I} - \boldsymbol{B})^{-1}\left(\boldsymbol{\Gamma}\boldsymbol{\xi}_{ij} + \boldsymbol{\zeta}_{ij}\right), \end{aligned} \quad (9)$$

where $\boldsymbol{I}$ is the identity matrix of dimension 6 by 6. It may also be noted that

$$(\boldsymbol{I}-\boldsymbol{B})^{-1}=\begin{bmatrix} 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \\ \beta_{2131} & \beta_{2231} & 1 & 0 & 0 & 0 \\ \beta_{2132} & \beta_{2232} & 0 & 1 & 0 & 0 \\ \beta_{2131}\beta_{3141}+\beta_{2132}\beta_{3241} & \beta_{2231}\beta_{3141}+\beta_{2232}\beta_{3241} & \beta_{3141} & \beta_{3241} & 1 & 0 \\ \beta_{2131}\beta_{3142}+\beta_{2132}\beta_{3242} & \beta_{2231}\beta_{3142}+\beta_{2232}\beta_{3242} & \beta_{3142} & \beta_{3242} & 0 & 1 \end{bmatrix}. \quad (10)$$

The resulting covariance matrix within an individual may be written as

$$Cov\left(\begin{bmatrix}\boldsymbol{x}_{ij}\\ \boldsymbol{y}_{ij}\end{bmatrix}\right)=\boldsymbol{\Sigma}_{ind}=\begin{bmatrix}\boldsymbol{\Lambda}_x\boldsymbol{\Phi}\boldsymbol{\Lambda}_x^T+\boldsymbol{\Theta}_x & \boldsymbol{\Lambda}_x\boldsymbol{\Phi}\boldsymbol{\Gamma}^T[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T\boldsymbol{\Lambda}_y^T \\ \boldsymbol{\Lambda}_y(\boldsymbol{I}-\boldsymbol{B})^{-1}\boldsymbol{\Gamma}\boldsymbol{\Phi}\boldsymbol{\Lambda}_x^T & \boldsymbol{\Lambda}_y(\boldsymbol{I}-\boldsymbol{B})^{-1}(\boldsymbol{\Gamma}\boldsymbol{\Phi}\boldsymbol{\Gamma}^T+\boldsymbol{\Psi})[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T\boldsymbol{\Lambda}_y^T+\boldsymbol{\Theta}_y\end{bmatrix}+\boldsymbol{\Lambda}_F\boldsymbol{\Lambda}_F^T. \quad (11)$$

Between twins in a pair the solution is

$$\begin{aligned} Cov\left(\begin{bmatrix}\boldsymbol{x}_{i1}\\ \boldsymbol{y}_{i1}\end{bmatrix},\begin{bmatrix}\boldsymbol{x}_{i2}\\ \boldsymbol{y}_{i2}\end{bmatrix}\right)&=\boldsymbol{\Sigma}_{MZ/DZ} \\ &=\begin{bmatrix}\boldsymbol{\Lambda}_x\boldsymbol{\Phi}_{MZ/DZ}\boldsymbol{\Lambda}_x^T & \boldsymbol{\Lambda}_x\boldsymbol{\Phi}_{MZ/DZ}\boldsymbol{\Gamma}^T[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T\boldsymbol{\Lambda}_y^T \\ \boldsymbol{\Lambda}_y(\boldsymbol{I}-\boldsymbol{B})^{-1}\boldsymbol{\Gamma}\boldsymbol{\Phi}_{MZ/DZ}\boldsymbol{\Lambda}_x^T & \boldsymbol{\Lambda}_y(\boldsymbol{I}-\boldsymbol{B})^{-1}\left(\boldsymbol{\Gamma}\boldsymbol{\Phi}_{MZ/DZ}\boldsymbol{\Gamma}^T+\boldsymbol{\Psi}_{MZ/DZ}\right)[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T\boldsymbol{\Lambda}_y^T\end{bmatrix} \\ &+\boldsymbol{\Lambda}_F\boldsymbol{\Phi}_{FMZ/FDZ}\boldsymbol{\Lambda}_F^T. \end{aligned} \quad (12)$$

Thus, for each twin pair we may construct an expected covariance matrix as

$$\boldsymbol{\Sigma}_{\boldsymbol{i}}=\begin{bmatrix}\boldsymbol{\Sigma}_{ind} & \boldsymbol{\Sigma}_{MZ/DZ}\\ \boldsymbol{\Sigma}_{MZ/DZ}^T & \boldsymbol{\Sigma}_{ind}\end{bmatrix}, \quad (13)$$

and use likelihood techniques to find a solution for the unknown parameters.

Estimating standardized regression coefficients

We have defined the covariance matrix for $\boldsymbol{\xi}_{ij}=\left(AP_{1ij},Ext_{1ij}\right)$ to be $\boldsymbol{\Phi}$, and for $\boldsymbol{\eta}_{ij}=\left(AP_{2ij},Ext_{2ij},AP_{3ij},Ext_{3ij},AP_{4ij},Ext_{4ij}\right)$ we may find

$$\boldsymbol{\Sigma}_{\eta}=Cov(\boldsymbol{\eta}_{ij})=Cov\left((\boldsymbol{I}-\boldsymbol{B})^{-1}(\boldsymbol{\Gamma}\boldsymbol{\xi}_{ij}+\boldsymbol{\zeta}_{ij})\right)=(\boldsymbol{I}-\boldsymbol{B})^{-1}(\boldsymbol{\Gamma}\boldsymbol{\Phi}\boldsymbol{\Gamma}^T+\boldsymbol{\Psi})[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T. \quad (14)$$

From these matrices we can find the variances of each latent construct, and calculate standardized regression coefficients. If β is the unstandardized regression coefficient where the dependent variable y is regressed on the independent variable x, the standardized regression coefficient β^* is defined as

$$\beta^*=\beta\frac{sd(x)}{sd(y)}, \quad (15)$$

where $sd(\cdot)$ is the standard deviation of the variable in question. For the current application this may look like

$$\beta^*_{1122}=\beta_{1122}\frac{\sqrt{\boldsymbol{\Phi}^{[1,1]}}}{\sqrt{\boldsymbol{\Sigma}_{\eta}^{[2,2]}}}, \quad (16)$$

where super-index refers to cell [row, column] in the matrix.

Standardized innovation effects

To get standardized innovation effects, meaning the b_A^2, b_C^2, and b_E^2 at each time-point, we divide with the variance from $\boldsymbol{\Phi}$ and $\boldsymbol{\Psi}$. For example, let b_{21A}^{*2} be the standardized b_{21A}^2;

$$b_{21A}^{*2} = \frac{b_{21A}^2}{\boldsymbol{\Psi}^{[1,1]}} = \frac{b_{21A}^2}{b_{21A}^2 + b_{21C}^2 + b_{21E}^2}. \quad (17)$$

Quantifying the correlation at each time-point

To be able to tease out which sources (i.e., *A*, *C* or *E*) the variation comes from first note that we may state a covariance matrix, within individual, for the structural model:

$$Cov\left(\begin{bmatrix}\boldsymbol{\xi}_{ij}\\ \boldsymbol{\eta}_{ij}\end{bmatrix}\right) = Cov\left(\begin{bmatrix}\boldsymbol{\xi}_{ij}\\ (\boldsymbol{I}-\boldsymbol{B})^{-1}(\boldsymbol{\Gamma}\boldsymbol{\xi}_{ij}+\boldsymbol{\zeta}_{ij})\end{bmatrix}\right) = \begin{bmatrix}\boldsymbol{\Phi} & \boldsymbol{\Phi}\boldsymbol{\Gamma}^T[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T\\ (\boldsymbol{I}-\boldsymbol{B})^{-1}\boldsymbol{\Gamma}\boldsymbol{\Phi} & (\boldsymbol{I}-\boldsymbol{B})^{-1}(\boldsymbol{\Gamma}\boldsymbol{\Phi}\boldsymbol{\Gamma}^T+\boldsymbol{\Psi})[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T\end{bmatrix}. \quad (18)$$

In this equation we may divide the sources of covariance into specific *A*, *C* and *E*-parts, as well as in time-points. Let superscript represent *A*, *C* or *E* coefficients, and let subscript represent time-point 1, 2, 3 and 4; At time-point 1 we may write

$$\boldsymbol{\Phi} = \boldsymbol{\Phi}_1^{\mathrm{A}} + \boldsymbol{\Phi}_1^{\mathrm{C}} + \boldsymbol{\Phi}_1^{\mathrm{E}}, \qquad \text{where e.g. } \boldsymbol{\Phi}_1^A = \begin{bmatrix} b_{11A}^2 & r_{A1}b_{11A}b_{12A}\\ r_{A1}b_{11A}b_{12A} & b_{12A}^2\end{bmatrix}. \quad (19)$$

Similarly, for subsequent time-points,

$$\boldsymbol{\Psi} = \boldsymbol{\Psi}_2^{\mathrm{A}} + \boldsymbol{\Psi}_2^{\mathrm{C}} + \boldsymbol{\Psi}_2^{\mathrm{E}} + \boldsymbol{\Psi}_3^{\mathrm{A}} + \boldsymbol{\Psi}_3^{\mathrm{C}} + \boldsymbol{\Psi}_3^{\mathrm{E}} + \boldsymbol{\Psi}_4^{\mathrm{A}} + \boldsymbol{\Psi}_4^{\mathrm{C}} + \boldsymbol{\Psi}_4^{\mathrm{E}}, \text{ where e.g.}$$
$$\boldsymbol{\Psi}_3^A = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & b_{31A}^2 & r_{A3}b_{31A}b_{32A} & 0 & 0\\ 0 & 0 & r_{A3}b_{31A}b_{32A} & b_{32A}^2 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\\ 0 & 0 & 0 & 0 & 0 & 0\end{bmatrix}. \quad (20)$$

It is thus possible to construct the stable and innovation sources of covariance. For example, at time-point 3 we include effects at time-points 1 and 2 in "stable" part, and effects at time-point 3 in "innovation" part. This can be written as

$$\text{stable}_3^A = \begin{bmatrix}\boldsymbol{\Phi}_1^{\mathrm{A}} & \boldsymbol{\Phi}_1^{\mathrm{A}}\boldsymbol{\Gamma}^T[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T\\ (\boldsymbol{I}-\boldsymbol{B})^{-1}\boldsymbol{\Gamma}\boldsymbol{\Phi}_1^{\mathrm{A}} & (\boldsymbol{I}-\boldsymbol{B})^{-1}(\boldsymbol{\Gamma}\boldsymbol{\Phi}_1^{\mathrm{A}}\boldsymbol{\Gamma}^T+\boldsymbol{\Psi}_2^{\mathrm{A}})[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T\end{bmatrix},$$
$$\text{innovation}_3^A = \begin{bmatrix}\boldsymbol{0} & \boldsymbol{0}\\ \boldsymbol{0} & (\boldsymbol{I}-\boldsymbol{B})^{-1}\boldsymbol{\Psi}_3^{\mathrm{A}}[(\boldsymbol{I}-\boldsymbol{B})^{-1}]^T\end{bmatrix}, \quad (21)$$

and we focus on the cells in time-point 3 (i.e., dimensions 5 to 6 in matrices) that are of interest. In the current paper we focus on the correlation therefore we would take cell [5,6] in the equations (21), and similarly for C and E to produce (let superscript [row, column] be the cell in a matrix)

$$\text{covariance}_3 = [\text{stable}_3^A]^{[5,6]} + [\text{stable}_3^C]^{[5,6]} + [\text{stable}_3^E]^{[5,6]} + [\text{innovation}_3^A]^{[5,6]} + [\text{innovation}_3^C]^{[5,6]} + [\text{innovation}_3^E]^{[5,6]}. \quad (22)$$

The covariance$_3$ may then made to correspond to the correlation by, for example, dividing by itself and multiply by the correlation obtained from standardizing the covariance matrix of the structural model shown in equation (18). Dividing the correlation into stable and innovation *A*, *C* and *E* is accomplished by seeing which proportion of the correlation that is accounted for by each of the parts in equation (22).

An alternative way to derive any variance or covariance is by using **eFigure 1b** and path tracing rules. This would be a tedious task, as would explicit solving of equation (22) in terms of scalar parameters (i.e., the parameters $b_{11A}^2, r_{A1}, \beta_{1121}$, et cetera), we therefore rely on numerically solving the problem using the resulting matrices produced in model fitting (i.e., the matrices $\mathbf{\Phi}, \mathbf{\Gamma}, \mathbf{B}$ and $\mathbf{\Psi}$).

eTables

eTable 2: Correlations, within individuals.

	Ext_{P1}	AP_{P2}	AP_{S2}	Ext_{P2}	Ext_{S2}	AP_{P3}	AP_{S3}	Ext_{P3}	Ext_{S3}	AP_{P4}	AP_{S4}	Ext_{P4}	Ext_{S4}
AP_{P1}	0.54[b]	0.56[c]	0.24	0.37	0.17	0.48[c]	0.21	0.37	0.14	0.40[c]	0.11	0.34	0.12
Ext_{P1}		0.42	0.19	0.58[c]	0.28	0.38	0.16	0.55[c]	0.25	0.30	0.09	0.42[c]	0.20
AP_{P2}			0.34[a]	0.60[b]	0.24	0.62[c]	0.32	0.48	0.23	0.46[c]	0.20	0.40	0.19
AP_{S2}				0.26	0.57[b]	0.30	0.53[c]	0.20	0.35	0.28	0.39[c]	0.20	0.31
Ext_{P2}					0.40[a]	0.46	0.24	0.68[c]	0.37	0.37	0.17	0.54[c]	0.29
Ext_{S2}						0.21	0.39	0.32	0.56[c]	0.23	0.30	0.32	0.43[c]
AP_{P3}							0.36[a]	0.59[b]	0.25	0.52[c]	0.18	0.47	0.20
AP_{S3}								0.27	0.57[b]	0.31	0.44[c]	0.29	0.40
Ext_{P3}									0.39[a]	0.43	0.15	0.59[c]	0.28
Ext_{S3}										0.23	0.31	0.36	0.51[c]
AP_{P4}											0.35[a]	0.61[b]	0.26
AP_{S4}												0.20	0.58[b]
Ext_{P4}													0.42[a]

Footnote: Values from Model 5 in **Appendix Table 1**. AP, attention problems. Ext, externalizing behavior. P, parent-rating. S, self-rating. 1, 2, 3, 4, time-points 1 (8-9 years old), 2 (13-14 years old), 3 (16-17 years old), and 4 (19-20 years old).

[a] Correlations within time-point and trait, between rater.

[b] Correlations within time-point, within rater, between traits.

[c] Correlations between time-points, within rater and trait.

eTable 3: Correlations between ratings and twins. MZ twins above diagonal, DZ twins below diagonal.

	AP_{P1}	Ext_{P1}	AP_{P2}	AP_{S2}	Ext_{P2}	Ext_{S2}	AP_{P3}	AP_{S3}	Ext_{P3}	Ext_{S3}	AP_{P4}	AP_{S4}	Ext_{P4}	Ext_{S4}
AP_{P1}		0.34	0.28	0.14	0.27	0.09	0.28	0.14	0.28	0.10	0.25	0.08	0.19	0.08
Ext_{P1}	0.24		0.28	0.14	0.48	0.17	0.28	0.14	0.46	0.20	0.23	0.08	0.32	0.16
AP_{P2}	0.12	0.22		0.20	0.41	0.13	0.34	0.17	0.36	0.12	0.26	0.09	0.25	0.11
AP_{S2}	0.08	0.11	0.12		0.19	0.22	0.17	0.26	0.14	0.16	0.20	0.23	0.16	0.18
Ext_{P2}	0.15	0.28	0.29	0.18		0.27	0.35	0.17	0.57	0.25	0.31	0.12	0.40	0.21
Ext_{S2}	0.07	0.11	0.12	0.16	0.19		0.13	0.19	0.22	0.26	0.15	0.18	0.22	0.23
AP_{P3}	0.13	0.22	0.18	0.09	0.23	0.09		0.20	0.44	0.15	0.34	0.12	0.33	0.14
AP_{S3}	0.06	0.08	0.10	0.15	0.12	0.12	0.09		0.20	0.23	0.21	0.25	0.22	0.23
Ext_{P3}	0.16	0.28	0.27	0.11	0.39	0.12	0.29	0.11		0.26	0.34	0.13	0.45	0.21
Ext_{S3}	0.05	0.08	0.10	0.13	0.16	0.14	0.09	0.14	0.15		0.15	0.18	0.23	0.30
AP_{P4}	0.11	0.19	0.15	0.11	0.23	0.13	0.16	0.10	0.25	0.09		0.21	0.41	0.20
AP_{S4}	0.05	0.08	0.11	0.15	0.14	0.11	0.12	0.15	0.10	0.13	0.09		0.16	0.25
Ext_{P4}	0.14	0.18	0.17	0.09	0.24	0.09	0.17	0.11	0.28	0.10	0.26	0.10		0.25
Ext_{S4}	0.07	0.10	0.10	0.13	0.14	0.12	0.10	0.15	0.11	0.14	0.13	0.17	0.09	

Footnote: Values from Model 5 in **Appendix Table 1**. AP, attention problems. Ext, externalizing behavior. P, parent-rating. S, self-rating. 1, 2, 3, 4, time-points 1 (8-9 years old), 2 (13-14 years old), 3 (16-17 years old), and 4 (19-20 years old).

eTable 4: Standardized genetic and environmental variance components.

	Time-point 8-9	Time-point 13-14	Time-point 16-17	Time-point 19-20
Additive genetic component in ADHD-like trait	**0.58** (0.43,0.71)	**0.55** (0.38,0.71)	**0.91** (0.56,0.98)	**0.83** (0.61,0.96)
Shared environmental component in ADHD-like trait	0.09 (0.00,0.20)	**0.19** (0.07,0.34)	0.00 (0.00,0.31)	0.00 (0.00,0.17)
Non-shared environmental component in ADHD-like trait	**0.33** (0.25,0.45)	**0.25** (0.17,0.35)	**0.09** (0.02,0.20)	**0.17** (0.04,0.33)
Additive genetic component in externalizing trait	**0.79** (0.66,0.93)	**0.38** (0.20,0.57)	**0.89** (0.51,0.97)	**0.83** (0.46,0.96)
Shared environmental component in externalizing trait	0.13 (0.00,0.26)	**0.48** (0.31,0.64)	0.00 (0.00,0.00)	0.00 (0.00,0.00)
Non-shared environmental component in externalizing trait	**0.08** (0.04,0.11)	**0.14** (0.09,0.20)	**0.11** (0.03,0.21)	**0.17** (0.04,0.35)
Correlation between genetic components	**0.63** (0.54,0.71)	**0.58** (0.35,0.79)	**1.00** (0.95,1.00)	**0.77** (0.65,0.92)
Correlation between shared environmental components	1.00 (-1.00,1.00)	**1.00** (0.82,1.00)	0.39 (-1.00,1.00)	0.89 (-1.00,1.00)
Correlation between non-shared environmental components	**0.60** (0.42,0.82)	**0.41** (0.19,0.61)	**1.00** (0.64,1.00)	**1.00** (0.41,1.00)

Footnote: Bold figures estimates where the confidence interval does not overlap the zero.

eTable 5: Parameter estimates from the full model. Parameter names as in **eAppendix B**.

Parameter	Estimate	Standard error	z-value
m_{APP1}	0.798	0.023	34.971
m_{ExtP1}	1.677	0.030	56.449
m_{APP2}	0.726	0.023	32.096
m_{APS2}	1.338	0.022	61.784
m_{ExtP2}	1.407	0.032	44.576
m_{ExtS2}	2.326	0.016	141.118
m_{APP3}	0.596	0.022	26.725
m_{APS3}	1.304	0.021	61.977
m_{ExtP3}	1.280	0.031	40.658
m_{ExtS3}	2.273	0.017	130.947
m_{APP4}	1.204	0.036	33.092
m_{APS4}	1.605	0.028	56.605
m_{ExtP4}	1.425	0.037	38.716
m_{ExtS4}	1.983	0.027	72.719
α_{APP1}	-0.233	0.030	-7.817
α_{ExtP1}	-0.191	0.038	-5.096
α_{APP2}	-0.198	0.029	-6.893
α_{APS2}	0.059	0.029	2.071
α_{ExtP2}	-0.164	0.038	-4.305
α_{ExtS2}	-0.014	0.023	-0.605
α_{APP3}	-0.092	0.029	-3.187
α_{APS3}	0.163	0.028	5.923
α_{ExtP3}	-0.078	0.038	-2.067
α_{ExtS3}	0.044	0.024	1.879
α_{APP4}	-0.143	0.045	-3.151
α_{APS4}	0.168	0.036	4.712
α_{ExtP4}	0.137	0.046	2.998
α_{ExtS4}	0.081	0.035	2.331
β_{1121}	0.494	0.065	7.598
β_{1122}	-0.021	0.043	-0.501
β_{1221}	0.136	0.040	3.419
β_{1222}	0.763	0.044	17.172
β_{2131}	0.614	0.056	10.94
β_{2132}	-0.053	0.049	-1.089
β_{2231}	0.061	0.031	1.948
β_{2232}	0.820	0.044	18.681
β_{3141}	0.845	0.101	8.407
β_{3122}	0.180	0.086	2.094
β_{3241}	0.030	0.057	0.526
β_{3242}	0.605	0.056	10.854
λ_{APS2}	0.439	0.028	15.757
λ_{ExtS2}	0.297	0.015	20.467
λ_{APS3}	0.598	0.037	16.294
λ_{ExtS3}	0.354	0.019	19.025

λ_{APS4}	0.461	0.036	12.695
λ_{ExtS4}	0.504	0.031	16.296
λ_{FAPP1}	0.092	0.037	2.461
λ_{FAPP2}	0.047	0.045	1.051
λ_{FAPP3}	0.297	0.039	7.694
λ_{FAPP4}	0.137	0.046	2.956
λ_{FExtP1}	-0.017	0.014	-1.181
λ_{FExtP2}	-0.056	0.034	-1.657
λ_{FExtP3}	0.366	0.061	6.043
λ_{FExtP4}	-0.011	0.038	-0.282
λ_{FAPS2}	0.426	0.018	24.254
λ_{FAPS3}	0.389	0.017	23.424
λ_{FAPS4}	0.337	0.020	16.658
λ_{FExtS2}	0.344	0.014	24.988
λ_{FExtS3}	0.355	0.014	26.031
λ_{FExtS4}	0.350	0.019	17.99
r_{FAPPMZ}	1.000	0.217	4.605
$r_{FExtPMZ}$	1.000	0.243	4.105
r_{FAPPDZ}	0.115	0.134	0.858
$r_{FExtPDZ}$	0.771	0.196	3.934
r_{FAPSMZ}	0.846	0.046	18.485
$r_{FExtSMZ}$	0.872	0.042	20.799
r_{FAPSDZ}	0.464	0.053	8.735
$r_{FExtSDZ}$	0.428	0.053	8.032
σ^2_{APP1}	0.046	0.025	1.863
σ^2_{ExtP1}	0.137	0.014	10.032
σ^2_{APP2}	0.077	0.011	6.985
σ^2_{APS2}	0.188	0.012	15.712
σ^2_{ExtP2}	0.116	0.012	9.858
σ^2_{ExtS2}	0.136	0.008	17.783
σ^2_{APP3}	0.079	0.017	4.732
σ^2_{APS3}	0.182	0.010	17.944
σ^2_{ExtP3}	0.067	0.035	1.935
σ^2_{ExtS3}	0.123	0.007	17.026
σ^2_{APP4}	0.170	0.027	6.276
σ^2_{APS4}	0.302	0.014	21.194
σ^2_{ExtP4}	0.182	0.024	7.550
σ^2_{ExtS4}	0.263	0.013	20.298
b_{11A}	0.490	0.024	20.797
b_{12A}	0.716	0.019	37.526
b_{21A}	0.348	0.030	11.572
b_{22A}	0.386	0.049	7.919
b_{31A}	0.285	0.017	16.622
b_{32A}	0.393	0.024	16.689
b_{41A}	0.467	0.028	16.857
b_{42A}	0.422	0.029	14.707

b_{11C}	0.192	NA	NA
b_{12C}	0.289	NA	NA
b_{21C}	0.206	0.039	5.319
b_{22C}	0.430	0.039	10.998
b_{31C}	0.000	0.047	0
b_{32C}	0.000	0.077	0
b_{41C}	0.000	0.116	0
b_{42C}	0.000	0.161	0
b_{11E}	0.373	0.037	10.111
b_{12E}	0.224	0.025	8.895
b_{21E}	0.235	0.026	8.939
b_{22E}	0.234	0.024	9.615
b_{31E}	0.089	0.025	3.524
b_{32E}	0.135	0.033	4.163
b_{41E}	0.209	0.062	3.356
b_{42E}	0.188	0.060	3.135
r_{A1}	0.629	NA	NA
r_{A2}	0.583	0.139	4.189
r_{A3}	1.000	0.083	12.049
r_{A4}	0.774	0.058	13.318
r_{C1}	1.000	NA	NA
r_{C2}	1.000	0.184	5.446
r_{C3}	0.387	NA	NA
r_{C4}	0.892	NA	NA
r_{E1}	0.600	0.087	6.856
r_{E2}	0.410	0.117	3.504
r_{E3}	1.000	0.357	2.798
r_{E4}	1.000	0.473	2.115

Footnote: NA, not applicable; NA appears when there were computational problems in finding a correct standard error.